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Controlled Temperature Tissue Fusion: Argon Laser Welding of Rat Intestine In Vivo, Part One

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Background and Objective: **Thermal denaturation of proteins is recognized as a rate process governed by the local temperature-time response. Since rate processes are exponential with temperature, laser-assisted tissue welding was performed with and without temperature feedback control (TFC) to investigate the efficacy of temperature feedback in enhancing the photothermal welding process in vivo.**
Study Design/Materials and Methods: **An automated system was developed for temperature feedback controlled laser irradiation. An experimental device incorporating co-aligned laser delivery and temperature detection was used to perform argon laser welded (with and without TFC) enterotomies. The weld strength and histology of laser welded and control sutured enterotomies were compared in an in vivo rat model. Animals (n = 41) were sacrificed at 1, 3, 7, and 21 days postoperatively, and the anastomotic site was removed for bursting/leaking pressure measurements and histological examination.**
Results: **Laser-welded (with and without TFC) and control sutured anastomoses in surviving animals healed comparably. Some laser-welded anastomoses without TFC ruptured spontaneously (4 out of 15) leading to the animals' death within the first 24–36 hours postoperatively. None of the animals in the other groups had this problem (control suture 0/6; laser with TFC 1 leak/8). The bursting/leaking pressures of the laser welded anastomoses were not significantly different than those of the sutured controls.**
Conclusion: **TFC improves the quality of laser-welded rat intestinal anastomoses in vivo in the critical first postoperative 36 hours. Lasers Surg. Med. 21:269–277, 1997.**

Key words: anastomosis; argon laser; dosimetry; feedback control; intestine; quasi-constant temperature control; temperature feedback; tissue fusion; tissue welding

INTRODUCTION

Lack of satisfactory objective criteria for optimal laser exposure parameters has been regarded as a major limitation of laser-assisted tissue welding (LTW). Experience has shown that excessive irradiation may result in more thermal damage than needed for the "laser-induced" bond, whereas inadequate heat deposition results in tissue dehydration without effective fusion [1–4].

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However, very few attempts have been made to enhance the photothermal welding process by some sort of feedback control [5–10].

The absorption of laser light results in the generation of a distributed heat source in tissue. The rate of heat generation [W/m^3] as a function of depth depends upon the optical penetration depth of the laser beam. Nevertheless, the magnitude of the distributed heat source decreases somewhat exponentially with depth. The resulting temperature profiles are governed by heat conduction in the tissue and thickness of the tissue relative to the optical penetration depth and thermal boundary conditions.

Infrared (blackbody) radiation emitted from tissue surface is increased as a result of laser-induced heat generation in tissue. The emissive power is given by $E(T) = \epsilon\sigma T^4$ where ϵ is the emissivity, σ is Stefan-Boltzmann constant, and T is surface temperature [K]. If emissivity is constant ($\epsilon \sim 1$), then a calibrated IR detector can be used to monitor surface temperatures (~20 μm thickness) during laser irradiation.

Thermal denaturation of tissue proteins has long been recognized as a rate process governed by the local temperature-time response [11,12]. These processes are exponential with temperature and linear with time. Feedback control of tissue surface temperature within a narrow margin is postulated to create a rather constant rate of denaturation and eliminate exponential increases in the rate of denaturation associated with excessive thermal insult, i.e., rapidly increasing temperatures (Fig. 1). In this figure, accumulated damage Ω increases at a constant rate when tissue temperature is held constant. Yet for linearly increasing temperature, the rate of increase in accumulated damage is exponential, suggesting an accelerated rate of thermal damage to tissue that can appear in milliseconds.

In a previous study, we hypothesized that tissue surface temperature is an indicator of tissue status during LTW and performed controlled temperature tissue welding of severed edges of fresh canine jejunum in vitro [13]. We found that laser-assisted intestinal anastomoses created in vitro were optimally strong at 90–95°C feedback control temperatures.

In this study, we further tested our hypothesis by welding rat small intestine segments in vivo with argon laser radiation with temperature feedback control (TFC) set to a control temperature of 90°C and without temperature feedback. Surface temperature was determined from measurement of emissive power using a calibrated IR sensor.

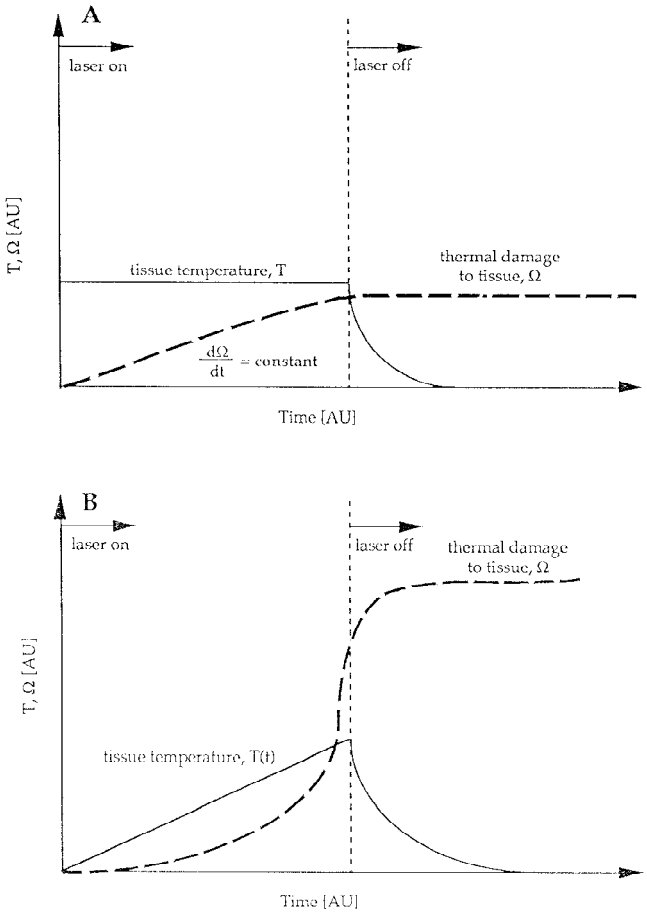

Fig. 1. Rate process model of thermal damage to tissue as a function of tissue temperature during and after laser irradiation: **(top)** constant tissue temperature while laser is on, and **(bottom)** ramp increase in temperature during laser irradiation.

MATERIALS AND METHODS

Surgical Procedures

Forty-one female Wistar rats (Harlan Sprague Dawley, Houston, TX), ages 4–7 weeks old, were used for experimentation. Rats were divided into three groups of 12 animals each for the following treatments: (1) all-sutured control anastomoses, (2) argon laser-assisted intestinal anastomosis with TFC at 90°C, and (3) LTW without temperature feedback. Each group was divided into four subgroups of three animals each for four different postoperative observation periods of 1 day, 3 days, 1 week, and 3 weeks. The remaining animals were used for repeat experiments. Surgical procedures were approved by the Animal Care

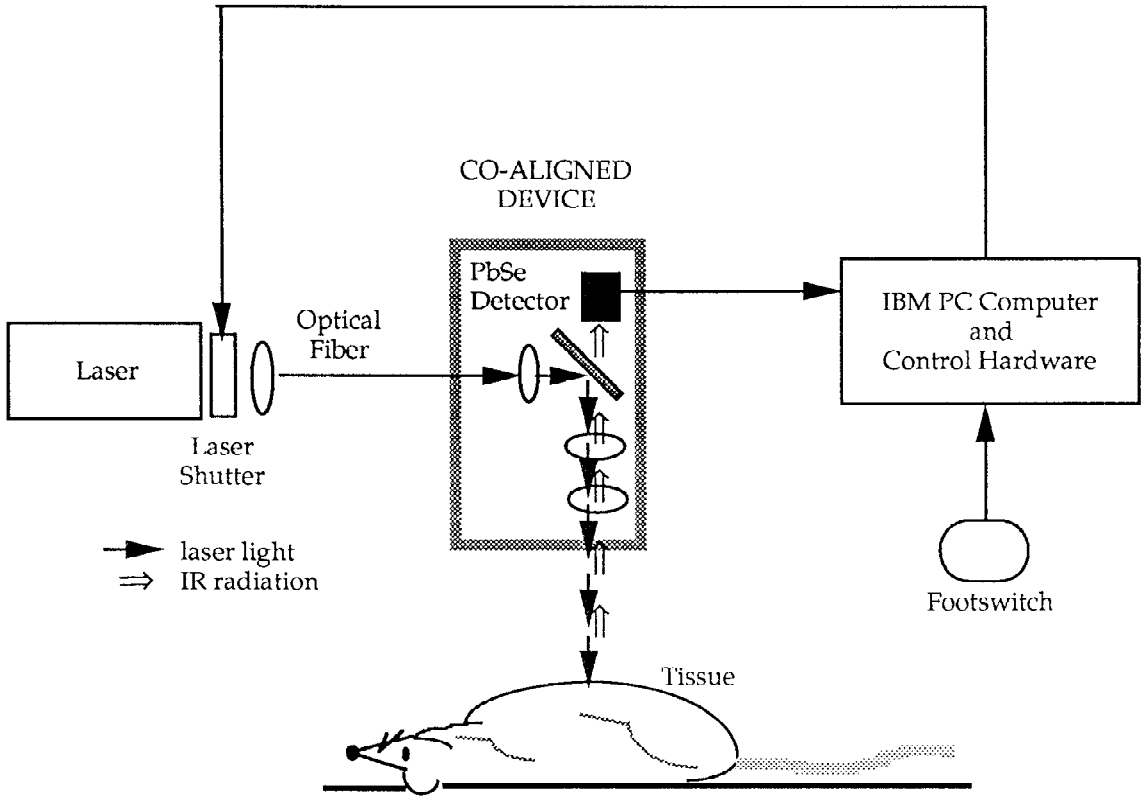

Fig. 2. Experimental setup for thermal feedback controlled tissue welding.

and Use Committee of University of Texas at Austin in accordance with the guidelines and regulations of the NIH/US Department of Agriculture NIH assurance number 1496.

The assignment of animals to a particular surgical method and the associated observation period was randomized. The rats were preanesthetized with fluothane. Anesthesia was introduced with a mixture of ketamine and rompun (4:3), 0.1 ml/100 gr intramuscularly. To prevent hypothermia, the animals were placed on a thermostatically controlled heated pad during surgery and postoperative recovery from anesthesia. All experiments were carried out using aseptic techniques.

A 2-cm-long midline laparotomy was performed and a small segment of small intestinal loop was exposed as described by van Dongen *et al.* [14]. The exposed segment was isolated and cut transversely with fine scissors. Before anastomosis the separated bowel ends were cleaned by removal of blood, blood clots, or succus entericus with cotton swabs moistened with phosphate-buffered saline (PBS). Subsequently, the bowel ends were dried with dry cotton swabs and approximated using 8-0 stay sutures. The number of sutures depended on the anastomotic method. Two stay sutures were placed 180° apart (symmetric biangulation) for suture controls and three sutures were placed 120° apart (symmetric triangulation) for laser-assisted anastomosis. Suture control anastomoses were closed with a total of 8–10 interrupted sutures (8-0). Laser-assisted anastomoses were completed as described below.

System Components

The experimental setup of the controlled temperature laser delivery system is shown in Figure 2. The operation of the system is based on an on-off control algorithm incorporating thermal feedback from a calibrated IR sensor (Infrared Industries, Orlando, FL) [7]. A laser shutter (nm Laser SC-1100/LS200FNS, Sunnyvale, CA) is placed on the path of the argon ion laser beam (Coherent, Innova 100, Palo Alto, CA) that operates at multiple visible wavelengths from 488 to 515 nm. The laser shutter is under the control of an IBM PC computer and associated control hardware, which is activated by a thermal feedback signal from the IR sensor. Note that the measured surface temperature at the irradiated air-tissue boundary is an indirect indicator of temperature

distribution in the tissue and is higher than the temperature in the bulk. Whenever tissue surface temperature exceeds a preselected control value, the laser shutter is closed. The shutter is reopened when tissue temperature falls below that preselected control value. Tissue surface temperature is maintained within a narrow band of temperatures throughout the welding procedure. The worst-case temperature resolution and response time of the system are ~1°C and ~50 msec, respectively [15].

In our device, the laser beam is focused onto the field of view (FOV) of the IR sensor. Co-aligned optics transmit both visible light and IR. Heating of optics due to laser radiation is negligible and does not change temperature readings significantly. It is assumed that tissue emissivity is the same as that of the IR calibration source and that it does not change throughout the laser-assisted procedure. Our device is oriented vertically. Prior to welding, an anastomotic site to be welded is aligned to the focal plane of the device using a very low power alignment beam. Using cotton swabs to expose the part of the enterotomy between two adjacent stay sutures, the specimen is moved sideways during laser irradiation to ensure adequate laser exposure along the full length of the enterotomy [2]. Surface temperature signals are collected and recorded from a 0.75 mm diameter spot at the center of the 1.5 mm diameter laser spot on the focal plane of the co-aligned device [15].

The feedback control system is activated and laser irradiation begins when the foot switch is depressed. Throughout an experiment, laser dosimetry is controlled entirely by temperature feedback as the operator moves the specimen. Currently, completion of welds requires a decision based upon visual observation as explained below.

Experimental Procedure

Intestinal welding was performed with and without TFC at 90°C. Using a low power beam, the enterotomy was brought into the focal plane of the co-aligned device. Laser power and laser delivery efficiency of the device were 1.75 W and 28%, respectively, resulting in an irradiance of 28 W/cm^2 at the focal plane of the co-aligned device. The anterior side of the enterotomy was "brush-welded" by slowly and continuously moving the specimen sideways. The tissue was irradiated and the laser beam was swept twice on the enterotomy until the apposed edges fused, i.e., "cooked" and blanched, a visual feedback mechanism also used by other researchers [7–9]. Irradiation of sutures was avoided as much as possible. The anastomosis was rotated using cotton swabs and the posterior weld was carried out in exactly the same way. One extra stay suture was placed when needed for better apposition of the bowel edges. There was no significant difference in bursting pressure results between animals with three or four stay sutures.

Once the rats were fully awake, they were placed individually in small cages and given water. Their regular diet (Harlan TEKLAD 4% Mouse-Rat Diet, Madison, WI) was gradually resumed ~12 hours postoperatively depending on their physical condition.

Rats were euthanized at the end of the assigned observation periods with an overdose of fluothane. A 5 cm length of intestine with the anastomosis in the middle was harvested and mounted on a glass tube, which in turn was connected to a custom made fluid pressure source. The open end of the intestine was clamped, and bursting/leaking pressures (BLP) were measured by increasing intraluminal pressure in each sample slowly infusing water at a steady rate of ~20 mm Hg/sec. The measurement end point was the first evidence of water escape through a leak or rupture point anywhere along the anastomosis. A section of normal intestine was also harvested from each animal to measure BLP of intact small intestine. Pressurized samples were immersed in 10% buffered formalin for fixation immediately after measurements were completed.

Histological Examination

Two tissue samples representative of each weld were dehydrated in graded ethanol solutions and xylene and embedded in paraffin. The samples were taken transverse to the welds along the longitudinal axis of the bowel segment. Representative 4-μm-thick sections stained with trichrome or hematoxylin & eosin were examined with light and transmission polarizing microscopy. Because all specimens had been at least partially ruptured by the bursting/leaking pressure test prior to fixation, bond integrity was not evaluated. The location and extent of thermal damage including hemorrhagic and coagulative necrosis, collagen hyalinization, and collagen and smooth muscle birefringence changes were sought in the 1-day specimens. The configuration and constituents of the wound tissues were examined for all specimens. The extent of necrosis and widths of gaps that developed between wound edges were measured for all specimens.

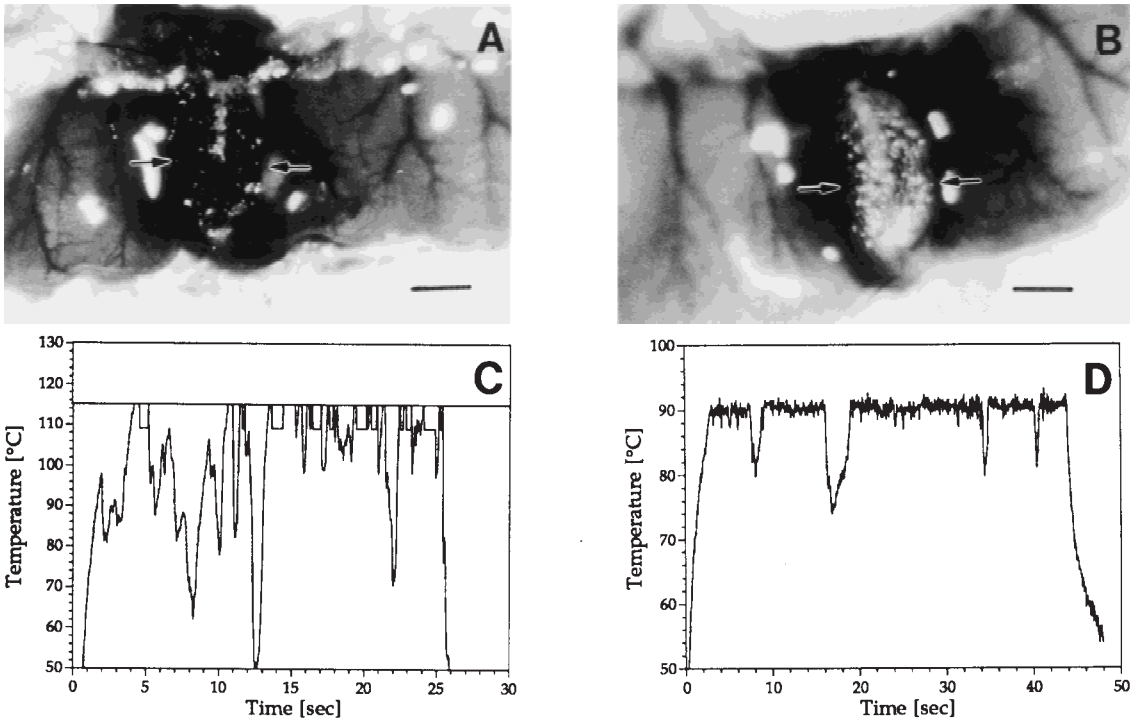

Fig. 3. Rat intestinal anastomoses immediately at the completion of surgery. [Bars = 1 mm] **A.** Laser-assisted anastomosis without TFC (arrows). The dark surface of the everted wound edges is due to caramelization and carbonization of the irradiated mucosal surface. **B.** Laser-assisted anastomosis with TFC (arrows). The irradiated mucosal surface (arrows) is whitened and the adjacent serosa is darkened with intramural hemorrhage. **C.** Temperature history of the laser-assisted anastomosis without TFC. The erratic profile shows numerous examples of wide temperature swings during the irradiation. **D.** Temperature history of the laser-assisted anastomosis with TFC. The dips in temperature occurred when cool, unwelded tissue was moved into the field of view.

Data Analysis

Statistical analysis of BLP measurements was carried out using Microsoft Excel® 4.0. Data were plotted on KaleidaGraph™ 3.0. Data were stored as averages with standard deviations and ranges.

EXPERIMENTAL RESULTS

Laser-assisted intestinal anastomoses provided an immediate fluid-tight seal when compared to the suture control anastomoses. The average "total exposure time" required to perform laser-assisted anastomoses with and without temperature feedback control was 142 ± 36 sec and 86 ± 20 sec, respectively (values are given as average ± standard deviation). In this study, "total exposure time" included laser-off times during feedback controlled laser irradiation.

Less thermal damage and carbonization were seen when laser irradiation was controlled by thermal feedback (Fig. 3). The overall results of this study are summarized in Table 1. Of the laser welded anastomoses without TFC, 27% spontaneously ruptured, and these animals died (n = 4) within the first 24–36 hours postoperatively. One laser-welded anastomosis with TFC in the 1-day group had a small leak and two anastomoses with TFC in the 3-day group broke during harvest even though they were intact at the time of euthanasia. Those experiments were repeated to obtain sufficient specimens to measure bursting pressure.

Physical Observations and Bursting/Leaking Pressure Tests

At 1 day, all anastomoses (sutured, laser-assisted with and without TFC) were very weak when compared to the BLP of intact normal rat small intestine, 255 ± 36 mm Hg (n = 37). The BLPs of all anastomotic groups ranged from 20 to 60 mm Hg, and there was no significant difference between anastomotic methods.

At 3 days, all anastomoses were somewhat stronger with the BLPs, ranging from 40 to 100 mm Hg. The BLPs of laser-welded anastomoses

TABLE 1. Average and ± Standard Deviation of Bursting/Leaking Pressures of Rat Small Intestinal Welds Performed With Sutures and Argon Ion Laser In Vivo

Observation period	Control sutured anastomosis	Argon laser assisted anastomosis without TFC	Argon laser assisted anastomosis with TFC at 90°C
1 day	3 specimens all intact 38 ± 19 mm Hg	3 specimens all intact 43 ± 21 mm Hg	3 specimens 1 small spontaneous leak, 2 intact 38 ± 18 mm Hg
3 days	3 specimens all intact 60 ± 35 mm Hg	6 specimens 4 ruptured, 2 intact 70 ± 14 mm Hg	5 specimens 5 intact, 2 broken[a] 47 ± 6 mm Hg
1 week	3 specimens all intact 263 ± 32 mm Hg	3 specimens all intact 213 ± 31 mm Hg	3 specimens all intact 253 ± 12 mm Hg
3 weeks	3 specimens all intact 293 ± 12 mm Hg	3 specimens all intact 260 ± 20 mm Hg	3 specimens all intact 277 ± 21 mm Hg

[a]2 broke in handling.

without TFC were slightly higher (60–80 mm Hg) than the BLPs of laser-welded anastomoses with TFC (40–50 mm Hg), but the differences were not quite significant ($P \sim 0.08$). The BLPs of sutured anastomoses ranged from 40–100 mm Hg in the 3-day group.

At 1 week, the BLPs of sutured and laser-assisted anastomoses with TFC at 90°C approximated the BLPs of intact bowel, 240–260 mm Hg and 240–300 mm Hg, respectively. Up to this day, all laser-assisted anastomoses burst open or leaked at or very close to stay sutures. Beyond day 7, they burst open at other locations than the stay sutures. The laser-assisted anastomoses without TFC were weaker (BLP: 180–240 mm Hg) than sutured and laser-assisted anastomoses with TFC ($P \sim 0.06$ and $P \sim 0.07$, respectively). There was no statistical difference between the BLPs of sutured and laser-assisted anastomoses with TFC.

At 3 weeks, all anastomoses were mechanically as strong as intact intestine, although BLPs of laser-assisted anastomoses without TFC tended to be lower than the other groups.

Histology Results

At 1 day, gaps appear between the wound edges in all specimens including the suture controls (Fig. 4). The gap widths are variable but are smallest in the sutured specimens. The wound edges are distorted by necrosis with slightly more extensive necrosis in the laser-assisted anastomoses without TFC than those with TFC (Table 2). Purulent and fibrinous exudates have filled the gaps and form a bridge between the wound edges. Omentum and mesentery wrap around the outer surfaces of the anastomoses in some specimens.

At 3 days, the necrotic wound edges have sloughed, leaving larger gaps that are partially plugged or covered with adherent omentum. The gaps are largest in the laser-assisted anastomoses with TFC and smallest in the sutured controls (Table 2). Early organization (healing) of the wounds has begun at the wound edges and in the luminal surfaces of the omental plug in all specimens.

At 1 week, fibrous scar tissue is forming and, qualitatively, the healing pattern of all three groups is comparable. The gaps continue to be larger in the laser-assisted welds formed with and without TFC compared to the suture controls.

At 3 weeks, the glandular mucosa tissue is beginning to grow over the omental fibrous scar tissue that fills the persistent gaps present in all specimens. Contraction of the collagenous scar tissue has made the gaps smaller, and all gaps are about the same size (Fig. 4).

DISCUSSION

In an in vitro study, Jenkins and associates [16] studied the effect of tissue temperature on Nd:YAG laser-assisted weld strength of postmortem aortic intima-media separations. They reported that adventitial tissue temperatures below 80°C were not associated with appreciable welds, a finding similar to our earlier observations [13]. In our in vitro study, argon laser-assisted canine intestinal welds were significantly stronger at 90–95°C TFC than they were at 80°C TFC. A limited number of argon laser-assisted rat intestinal welds were created at 80°C, but they eventually

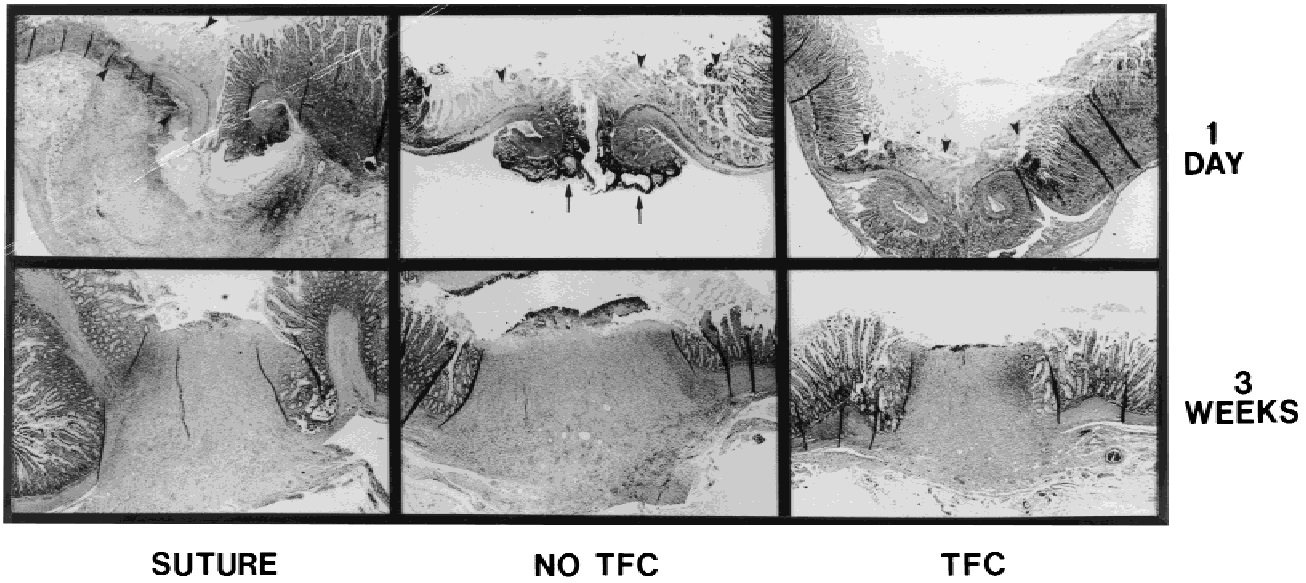

Fig. 4. Histologic appearances of representative anastomoses at 1 day **(top panel)** and 3 weeks **(bottom panel).** At 1 day, transmural coagulative and hemorrhagic necrosis (arrow heads) is most extensive in the laser anastomosis without TFC but is also present at one side of the featured suture anastomosis and in the laser anastomosis with TFC. Omentum covers the serosal surface of the one day sutured anastomosis. Dessication and water vacuoles distort the tissues of the laser anastomosis with no TFC (arrows), therefore showing the severe damage that can occur without temperature control. At 3 weeks, the wound gaps of all anastomoses **(center of picture)** are filled with fibrous and vascular granulation tissue characteristic of normal healing. [Hematoxylin and eosin stains. Original magnifications: 1 day specimens, 8× and 3 weeks' specimens, 6.25×.]

opened up <4 hours postoperatively, and the animals were sacrificed. In the light of those observations, we chose to perform laser-assisted rat intestinal anastomoses at 90°C surface control temperature.

The temperature system of Poppas et al. [9] used to weld porcine skin incisions closely resembles the system used for these experiments in terms of calibrated detection of emissive power with a detector that has a FOV smaller than the laser spot size. Their spot size and concentric detector FOV were 1.0 mm and 0.4 mm, respectively. The welding wavelength was 1.32 μm. Their acute tensile strength data indicated that maximum strengths were obtained with a control temperature of 95°C. However, at 3 and 8 days, tensile strengths for welds at 65°C and 76°C were higher than (1) welds formed at higher temperatures, and (2) sutured control incisions [9]; 65°C was considered the minimum tissue surface control temperature for robust welds.

Some of the differences in the two experiments are listed in Table 3. Penetration depth of the laser beam relative to the thickness of incisions was less for the argon/intestine than the Nd:YAG (1.32 μm)/skin. In both experiments, the temperature within the tissue was less than the surface temperature because of the air-tissue

TABLE 2. Extent of Necrosis and Wound Gap Size in Rat Small Intestine Walls Performed With Sutures and the Argon Laser*

	1 Day*		3 Days	1 Week	3 Weeks
	Necrosis (mm)	Gap width (mm)	Gap width (mm)	Gap width (mm)	Gap width (mm)
Suture control	0.9	0.2	1.5	0.8	1.9
	n = 4	n = 4	n = 6	n = 5	n = 5
Laser without temperature control	1.3	1.6	3.5	4.5	1.9
	n = 10	n = 3	n = 2	n = 4	n = 5
Laser with temperature control	1.2	2.1	5.2	5.0	1.9
	n = 3	n = 1	n = 3	n = 3	n = 7

*Necrotic tissue present at Day 1 is sloughed by Day 3.
n = number of measurements.

boundary condition. Undoubtedly, the temperature gradient in the intestine was much larger (4–6 times) than for the pig skin. However, the major differences in early weld strengths at 65°C and 75°C were (1) the use of an albumin solder by Poppas et al. [9], and (2) the different tissue components forming the welding surfaces in the two different organs.

The albumen solder provides an additional protein matrix intermixed with the dermal collagen. Thermal coagulation of both contributes to the acute bond strength. The fusion product of our mucosa to mucosa intestinal anastomosis seems to consist of thermally coagulated tissue proteins including mucus and superficial cells of the glandular mucosa, an entirely different welding environment. Since collagen is not present in the mucosal surface, thermal collagen denaturation plays no role in welding the rat intestine using our surgical approach [14]. However, laser-assisted anastomoses using apposition of collagenous serosal surfaces would involve tissue adhesions due to thermal denaturation of collagen similar to mechanisms proposed by others [17–19]. Therefore, close comparisons of control temperature/mechanical strength relation for the two studies indicate interesting trends but no firm conclusions because of the diverse experimental and tissue conditions.

This study evaluates the application of TFC for dosimetry control in LTW in real-time. Our findings indicate that TFC controls laser-induced thermal damage. Although these welds are initially weak, they were sufficiently stabilized to resist spontaneous rupture in surviving animals. Even though controlling tissue surface temperature increases the time required for LTW, the rate of denaturation is reduced as predicted in Figure 1. Therefore, by avoiding unexpected, rapid changes in the condition of the tissue, irradiation can be terminated at a desired visual endpoint which in these experiments was an intact weld.

CONCLUSIONS

Real-time dosimetry control via thermal feedback from a calibrated infrared sensor is feasible for laser-assisted tissue fusion. Although LTW of intestinal anastomosis using an argon ion laser does not provide significant benefits over sutured anastomosis in our rat model, with TFC there is clearly less thermal damage and the welds are weak but stable when compared to laser-assisted welds without TFC.

This report discusses an experimental coaligned setup for dosimetry control during LTW. For clinical trials, a more compact practical setup, probably relying on optical and thermal fibers, needs to be developed. A combination of optical and thermal feedback is also being considered for better dosimetry control.

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TABLE 3. Comparisons of Experimental Conditions for Data of Çilesiz et al. and Poppas et al.

	Çilesiz et al.	Poppas et al.
Animal	Rat	Pig
Tissue	Intestine	Skin
Incision	Complete transverse cut	2 cm incision
Stay sutures	3 or 4	1 (cut at end of procedure)
Albumin solder	No	Yes
Wavelength	All lines argon	1320 nm
Optical penetration depth	0.3–0.4 mm	1.7 mm
Tissue thickness	~1.5 mm	>3 mm

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